PATENT
Docket No.: **57953/1201 (ZUC01-02US)**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Dorothea Zucker-Franklin	Examiner: John Kim
Serial No.	:	10/796,747	
Cnfrm. No.	:	2516	Art Unit: 1723
Filed	:	March 9, 2004	
For	:	DEVICES AND METHODS FOR REMOVAL OF LEUKOCYTES FROM BREAST MILK	

REQUEST FOR RECONSIDERATION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In view of the following remarks, reconsideration of the April 23, 2007, office action is respectfully requested.

The benefits of breast feeding are well recognized and require no elaboration. Volumes have been written on this subject. Apart from the nutritional, physiologic, and psycho-social values pointed out in numerous publications, breast feeding incurs no financial burden. However, as is true in other areas of medicine, what seems physiologic or "natural" is not always flawless. Breast milk is a case in point. In general, the immunoglobulins contained in breast milk are likely to be protective to the infant, who has not yet been exposed to environmental microorganisms or other pathogens. However, immunoglobulins in breast milk may include antibodies directed against the infant's red blood cells in cases where mother and infant are not Rh or ABO compatible. Breastfeeding of neonates with alloimmune hemolytic disease, be it attributable to Rh or ABO incompatibility, would add insult to injury and, therefore, it is usually interdicted.

It is not as commonly recognized that breast milk also contains a large variety of cells. While some of these cells represent ductal epithelial cells and their fragments, the

presence of leukocytes is by no means insignificant. Colostrum contains about 10,000 lymphocytes per cubic mm. T-lymphocytes make up about 2000 cells per cubic mm. Similar values have been reported by others. Because peptic enzyme activity and acid secretion are very low in newborn infants, lymphoid cells survive in their stomach and intestine. In addition, lymphocytes are known to traverse the mucosal wall. Therefore, breastfed infants may be tolerant to maternal antigens. It has even been claimed that maternal renal allografts have a better survival rate in individuals who were breastfed than in individuals who were not.

More importantly, lymphocytes may carry microorganisms, such as retroviruses. This pertains particularly to the Human Lymphotropic Virus Type I ("HTLV-I"). Soon after the discovery of this virus, which causes leukemias, lymphomas, and a variety of inflammatory diseases, it was realized that this virus is transmitted sexually from male to female, by blood transfusion, and from mother to infant by breast feeding. Transmission of HTLV-I to animals via breast milk obtained from sero-positive persons had also been shown. Therefore, breast feeding by mothers who were shown to have antibodies to HTLV-I was prohibited in Japan. In the United States, HTLV-I antibody positive blood has not been used for transfusion since 1988.

Perhaps of even greater significance is, that in areas of the world where the virus is not endemic, *e.g.*, in the United States, the prevalence of individuals who do not carry intact viruses but who, nevertheless, have the Tax sequence of HTLV-I in their lymphocytes usually goes unrecognized. Such individuals test serologically negative for antibodies to the structural proteins of the virus. However, it should be appreciated that Tax DNA and its gene product p40Tax are responsible for the pathogenicity of this virus. This was first realized with the observation that patients with the cutaneous T cell lymphoma Mycosis Fungoides harbor the Tax sequence of HTLV-I in their peripheral blood and skin-infiltrating lymphocytes without having antibodies to the structural proteins of the virus. In fact, some of the healthy relatives of these patients had served as blood donors, since they were found to be serologically negative for antibodies to the structural proteins of the virus by western blot, a test still being used in U.S. blood banks to rule out infection with HTLV-I. It has been shown that about 8% of blood donors in New York City carry HTLV-I Tax in their lymphocytes. In some inflammatory diseases, *e.g.*, rheumatoid arthritis, the prevalence of HTLV-I Tax positivity is at least 3 times higher than in healthy individuals. This would, of course, also

pertain to breastfeeding women. Moreover, it has been demonstrated that transfusion of Tax-positive human lymphocytes into rabbits renders these animals HTLV-I positive.

For all the reasons cited in the foregoing (allo-immunization, infections, etc.), it would be beneficial to eliminate leukocytes from breast milk.

The present invention is directed to achieving these objectives.

Claims 7–26 are withdrawn. Claims 1–26 are pending.

The rejection of claims 1–6 under 35 U.S.C. § 103(a) for obviousness over U.S. Patent No. 2,364,866 to Meynier, Jr., ("Meynier") in view of U.S. Patent No. 5,229,012 to Pall et al. ("Pall") and Michie et al., "Breast Feeding and the Risks of Viral Transmission," *Arch. Dis. Child.* 84:381–2 (2001) ("Michie"), is respectfully traversed.

Claims 1–6 of the present invention relate to a nipple shield device for removing leukocytes from breast milk that includes a nipple shield and a filter. The nipple shield has a base and a protrusion that is shaped to conform to a mammalian female areola and nipple, where the protrusion has one or more holes permitting intake of breast milk by an infant. The filter is attached to the nipple shield at a location permitting removal of leukocytes from breast milk.

Meynier relates to a nipple shield that includes a flared or enlarged portion which fits closely by suction upon the mother's breast, and a nipple receiving portion which is integral centrally with the enlarged portion and which is of substantially the same size internally as the natural nipple. The nipple is provided with one or more openings at its outer end for the passage of fluid therefrom.

Pall relates to a device and method for depleting the leucocyte content of whole blood and products derived therefrom. Pall teaches that some viruses (*e.g.*, cytomegalovirus, Graft virus, HIV, and HTLV1) are transmitted during blood transfusions, and, since "several" of these viruses reportedly reside in the leucocytes, removing leucocytes from packed red cells is beneficial to prevent viral infection by transfused blood.

The Pall device includes a fibrous leucocyte adsorption/filtration filter that, *inter alia*, has a critical wetting surface tension ("CWST") of from 53 to about 80 dynes/cm. Filters having a diameter of 47.6 mm or 88.9 mm are specifically disclosed. In relation to CWST, Pall teaches that liquids with surface tensions lower than the CWST of a medium will wet the medium and, if the medium has through pores, will flow through it readily. Liquids with surface tensions higher than the CWST of the medium will not flow at all at low

differential pressures, but will do so if the pressure is raised sufficiently. The greater the difference between the surface tension of the fluid, the greater the amount of pressure required to induce flow.

The Pall filter is contained in a housing that defines a fluid flow path between an inlet and an outlet. In use, blood is drawn from a donor into a collector bag. The collector bag is placed in a centrifuge and spun, forming packed red cells at the bottom of the bag. The collector bag is then placed in a plasma extractor, decanting the plasma and most of the platelets, and leaving packed red cells in the bag. These packed red cells are then forced to pass through the Pall filter using pressure from a pressure cuff or the plasma extractor.

Michie discloses that retroviruses including HIV-1, HTLV-1, and HTLV-2 are transmitted by breast milk, but that there is a lack of precise knowledge as to the mechanisms whereby virus infects the breast feeding infant. It teaches that retroviruses may infect the mammary epithelial cell antenatally, and that they are also found free in solution and within milk monocytes. Michie further states that, although one might conceivably remove cell associated virus by filtering, free viral particles are difficult to eliminate.

The United States Patent and Trademark Office ("PTO") has taken the position that it would have been obvious in light of Pall and Michie to include a leucocyte filter in the Maynier nipple shield. Applicants respectfully disagree, because none of the cited references teaches or suggests filtering leucocytes from breast milk, let alone a device of the present invention.

First, none of the cited references, alone or in combination, teaches or suggests filtering leucocytes from breast milk.

Meynier says nothing about filtering at all, let alone filtering leucocytes from breast milk.

While Pall may provide a motivation to remove leucocytes from *blood*, it does not teach or suggest removing leucocytes from *breast milk*. None of the cited references teaches or suggests that viral transmission by blood transfusion is at all similar to viral transmission by breast milk, or that the leucocytes present in blood are also present in breast milk. Thus, there would have been no motivation to apply Pall's method to breast milk.

Michie does not overcome these deficiencies. Michie states that "one *might conceivably* remove cell associated virus by filtering breast milk." This passage has been cited by the PTO as teaching the removal of virus by filtering breast milk. It does not. Not

only is this language speculative at best, Michie in fact teaches away from filtering, because, according to Michie, filtering monocytes from breast milk would not prevent virus transmission. In particular, Michie teaches that retroviruses, although present in milk monocytes, are also found free in milk solution, and that removing cell associated virus by filtering would not eliminate free viral particles. Thus, Michie does not teach that filtering out virus-associated cells would remove virus from breast milk. Instead, Michie suggests pasteurization, vaccination, nevirapine treatment, establishing pasteurized milk banks, and wet nursing practices as possible solutions to vertical viral transmission by breast feeding.

For these reasons, none of the cited references, alone or in combination, provides a motivation to filter leucocytes from breast milk. Accordingly, there would have been no motivation to attach a leucocyte filter to the Meynier nipple shield.

Second, even if a skilled artisan would have been motivated to filter leucocytes from breast milk, which applicants do not concede, none of the references, alone or in combination, teaches or suggests the nipple shield of the present invention.

Meynier and Michie do not teach or suggest a leucocyte filter, let alone one attached to a nipple shield as presently claimed.

Although Pall discloses a leucocyte filter, there would have been no motivation to attach the Pall leucocyte filter to the Meynier nipple shield.

The Meynier nipple shield is the same size internally as the natural nipple, which averages around 16 mm during lactation, Ramsay et al., "Anatomy of the Lactating Human Breast Redefined with Ultrasound Imaging," *J. Anat.* 206:525–34 (2005) (Exhibit 1). Pall, however, discloses filter devices that have in internal diameter of around 47.6 mm or 88.6 mm, at least nearly triple the diameter of the Meynier nipple shield. Furthermore, Pall teaches that its filter is preferably large in cross sectional area perpendicular to the flow path of the filtered fluid, which teaches away from using the Pall filter in smaller diameter devices.

Additionally, Pall teaches a device in which fluid is forced to pass through the filter at an exemplary pressure of about 0.4 Kg/cm^2 (*i.e.*, about 294.22 mmHg). With the Meynier nipple shield, on the other hand, breast milk is drawn directly from the mother to the baby, using nothing but suckling to draw the fluid through the nipple shield. However, the average suckling pressure in humans is only about 50 mmHg, and the maximum suckling pressure is less than 200 mmHg. Prieto et al., "Sucking Pressure and Its Relationship to Milk

Transfer During Breastfeeding in Humans," *J. Reprod. Fertil.* 108:69–74, abstract (1996) (Exhibit 2). This is far lower than the pressure taught by Pall.

Finally, Pall teaches that it is highly undesirable in a leucocyte depletion device to use a medium with a CWST more than about 15 to about 20 dynes/cm lower than the liquid's surface tension. Since none of the cited references discloses the surface tension of breast milk, it cannot be determined from these references whether the Pall filter could be used to filter breast milk at all, let alone whether one could do so with the Pall filter attached to the Meynier nipple shield.

For these reasons, Meynier, Pall, and Michie fail to teach or suggest a nipple shield shaped to conform to a mammalian female areola and nipple, and a filter attached to the nipple shield at a location permitting removal of leucocytes from breast milk, as presently claimed.

For all of the these reasons, the rejection of claims 1–6 for obviousness over Meynier, Pall, and Michie is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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